

Exhibit 45

The insulin market is heading for a shakeup. But patients may not benefit



By [Rebecca Robbins](#)¹ Oct. 14, 2016



A high-speed production line of insulin at the Novo Nordisk factory in Chartres, France. *Francois Monier/AFP/Getty Images*

The insulin market, dominated by old drugs that have [skyrocketed in price](#)³, is on the verge of a shakeup.

The first “follow-on” insulin for diabetics, similar to a generic medication for synthetic drugs, will hit the market in December. It’s expected to be followed in the coming months and years by a wave of new follow-on and “biosimilar” insulins that have the same protein structures as brand-name products.

Experts predict that these new insulins will carry lower prices — but it’s far from certain that the competition will drive down costs overall.

The stakes are high: About 6 million Americans with diabetes [use insulin](#),⁴ either alone or in combination with an oral drug. The annual cost of insulin [reached \\$736](#)⁵ per patient in 2013, up threefold since 2002. Diabetes medicines, including insulin, are the second most expensive category of prescription drugs, [according to Express Scripts](#)⁶, the big pharmacy benefits manager.

Here’s what you need to know about how insulin prices got so high — and what you should expect from the coming shifts in the market.

What’s on the market now?

The vast majority of diabetics who need insulin choose from a menu of a half-dozen “analog” brands, which are chemically altered from natural human insulin. They’re manufactured by just three different drug makers: Novo Nordisk, Sanofi-Aventis, and Eli Lilly. Some are long-acting insulins, injected once or twice a day; others act rapidly and patients inject or deliver them with a pump as needed. Many patients use both.

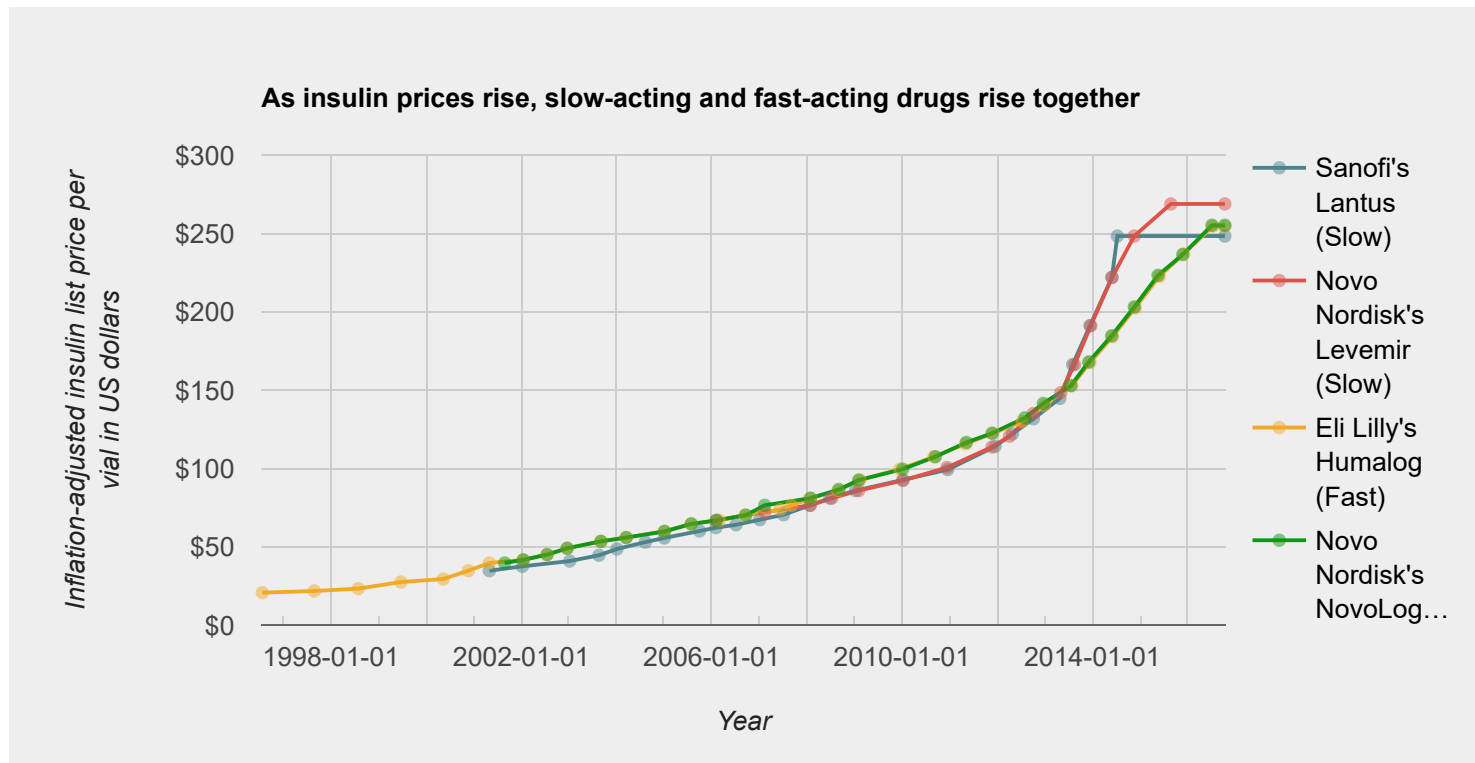
A few of these products — like Novo Nordisk’s Tresiba and Sanofi’s Toujeo, which are both long-acting — have only been on the market a matter of

months, and aren't yet widely used. But the others have generally been around for at least a decade, and sell for list prices in the neighborhood of \$250 per vial. (The actual price that consumers and insurance companies pay is often much lower.)

A small percentage of diabetics use lower-priced "human" insulin brands, which are manufactured to mimic the insulin naturally made by the human body. Walmart, for instance, sells such a product (under the brand name ReliOn) for less than \$25 per vial. A Walmart spokesperson didn't respond to a query about how much of it the retailer sells.

With all that competition, why aren't prices dropping?

You'd expect competition to lower prices, but it hasn't worked out that way in the insulin market. If you track the list price of the best-selling analog brands in recent years, you'll see something remarkable: Prices of directly competing brands have been going up in lockstep by the amount at about the same time, in a practice known as "[shadow pricing](#)".⁸



So what's going on here? Experts say there are a number of factors at play.

Drug makers have said they don't collude on pricing in advance, but move to match their competitors' price hikes.

They point out that the net price — how much revenue they get from each sale — has been rising fairly modestly, as detailed in a recent report from the [Wall Street Journal](#)⁹.

The list price has been going up more steeply, in part because the middlemen who stand between the manufacturer and the patient — such as pharmacy benefits managers — demand ever-larger rebates.

“Rest assured there is great competition on insulin pricing” — but that's taking place at the net pricing level, said Mike Mason, vice president of Lilly's US diabetes business.

Another key factor: Compared to other drug categories like cholesterol or pain relief medicines, there's an unusual degree of reluctance among patients and physicians to switch between insulin brands. “These products are not completely substitutable, and manufacturers perceive that, and so they exercise monopoly power over pricing,” said Rena Conti, a health economist at the University of Chicago.

Other reasons that analog insulin prices have not declined: Demand is up. And there are increasing regulatory demands on the manufacturing process.

The cumulative effect of many gradual price hikes “snuck up on people,” said Dr. William Herman, who practices internal medicine at the University of Michigan. “The prices just went up and up and up.”

Why are we only just now getting ‘generic’ insulin?

Insulin has been around for nearly a century. But it's hard to develop knock-off biological products, and for a long time there wasn't a lot of incentive to do so.

Key here is the difference between synthetic drugs like statins and those made from biological materials like insulin. It's easy to develop chemically equivalent copies, or generics, of the former. By contrast, biological materials are more variable and, as a result, more complicated to duplicate.

Patents have also a lot to do with it. For a long time, insulin makers have been able to make incremental improvements on their branded drugs that allowed them to extend the patent life on their products. But for some insulins, that gambit has run its course.

The patent expired last year on Sanofi's drug Lantus, known to scientists as glargine. And Lilly's rapid-acting insulin, sold as Humalog, saw its compound and formulation patents expire in 2013 and 2014, respectively.

With the patents expiring, some manufacturers are rushing to make "generic" versions of their competitors' branded insulin. Lilly, for instance, has made an approved version of Sanofi's glargine, known as Basaglar.

What's going to happen when the first 'generic' insulin hits the market?

Basaglar will hit the market on Dec. 15. The company hasn't set a price yet, but analysts expect Basaglar to carry a list price 10 to 20 percent lower than Lantus, which is listed at about \$250 per vial.

[CVS](#)¹² and [Express Scripts](#)¹³ have both said they'll list Basaglar on their formularies. (CVS, notably, said it would no longer cover Lantus.)

Experts don't expect Basaglar's launch to mean much in the way of cost savings for patients, though they say it could mean big rebates and discounts for middlemen within the black box of drug pricing.

For patients without insurance or for those facing high deductibles or copays, “I don’t think they’re going to see major improvements,” said Dr. Irl Hirsch, an endocrinologist at the University of Washington.

OK, then, will prices go down when more ‘generic’ insulins become available?

Don’t bet on it, though we’ll probably see slightly more savings.

The likeliest candidate to follow Basaglar onto the market is another follow-on glargine product, from Merck. The drug maker in August filed for approval with the Food and Drug Administration, and Merck spokeswoman Doris Li said the company expects to receive a decision in the first half of next year.

Sanofi is working on a follow-on insulin that would mimic Lilly’s Humalog; that’s in late-stage clinical trials, according to Sanofi spokeswoman Anna Robinson. Mylan also has several knockoff insulin products in the pipeline.

Meanwhile the so-far futile quest continues for what experts say would be a tremendous innovation — an insulin pill. Novo Nordisk, for instance, has such a molecule in early stage trials.

So are insulin prices just going to keep going up forever?

Probably not; in fact, there are already signs they’re tapering off. Express Scripts [reported](#)⁶ that the unit cost of Lantus dropped by nearly 14 percent last year.

“The manufacturers are beginning to feel the heat with respect to the prices of insulin,” Herman said.

But Herman emphasized that questions remain unanswered about how to properly price a drug that many diabetics need to stay alive. “What is the value

of insulin? It's the value of a human life," he said. "So how do you set a fair market price on it?"

About the Author



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